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EASTMAN

MR 61431

August 15, 2002

Ms. Christine Todd Whitman, Administrator
U.S. EPA
P.O. Box 1473
Merrifield, VA 22116

Attn: Chemical Right-to-Know Program

RE: HPV Chemical Challenge Program, AR-201

Dear Ms. Whitman:

This letter is submitted by Eastman Chemical Company ("Eastman") in response to comments received from the Environmental Protection Agency ("EPA") dated August 13, 2002 following EPA's review of the test plan and robust summaries for 3-Methylbutanone [Methyl isopropyl ketone; (MIPK); CAS No.: 563-80-4]. I would like to thank the EPA for its review and welcome the recognition of its completeness and fulfillment of Eastman's obligation to this chemical in the HPV program.

Below are the EPA's comments to our test plan and various robust summaries, and our responses:

Chemistry (melting point, boiling point, vapor pressure, water solubility, and partition coefficient).

1. "The submitter provided estimated values for all endpoints. EPA disagrees with the submitter's approach to these endpoints. Critical endpoints such as water solubility and vapor pressure should be measured values. The use of estimated values increases the level of uncertainty in subsequent modeling such as the fugacity calculation."

According to the EPA guideline – The Use of Structure-Activity Relationships (SAR) in the High Production Volume Chemicals Challenge Program. OPPT, US EPA (1999) – "In the event that neither measured data nor reference book values are available, estimations using an appropriate model will be accepted for all physicochemical endpoints." Accordingly we utilized the estimation models within the EPIWIN program, distributed by the EPA, to fulfill the required physical and chemical properties.

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity).

1. *"Fugacity.* The input values used in the fugacity calculation need to be added to the robust summary."

The input values utilized in this model were default values obtained from the EPIWIN program. Since all the physical chemical summaries also consisted of computer model estimations any values listed would be one in the same and will vary with future refinements of the models.

Ecotoxicity (fish, invertebrates, and algae).

1. "The acute algal toxicity study, with mean measured concentrations, is adequate. However, the fish and daphnia acute toxicity studies are inadequate. These studies were performed under static conditions with nominal concentrations, and as reported in the algal study (up to 78.2 % loss), there was most likely a significant loss of test material through volatilization. Because of this substance's volatility, EPA suggests that all testing be done with measured concentrations in a closed system with no head space. Testing should follow the Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures (OECD, June 2000-available on the OECD website at http://www.oecd.org./ehs/test/monos.htm)."

Eastman disagrees that the data for fish and *Daphnia* are inadequate and that new tests need to be completed in accordance to current guidelines. The basis for this comment appears to be due to the significant difference observed between the nominal versus measured concentration values in the algal study. The significance of this observation and the ability to transfer the same effect to other ecotoxicity studies is not always that straightforward. For example, an identical effect occurred between the nominal and measured concentrations in an algal study with methyl n-amyl ketone (MAK; CAS NO.: 110-43-0) (See MAK HPV Test Plan). In this study a large difference also occurred between the nominal and measured concentrations in the algal study but this phenomena was not present in either the fish or *Daphnia* studies where the nominal and measured concentrations were very similar. We believe the current studies on MIPK also contain significant merit and predictive potential based on the results of the computer model within EPIWIN that estimates its half-life from a model lake to be 6.2 days. Thus, it is likely that a significant amount of material would have been present in our test system within the timeframe of the study to see some effects if it were acutely toxic to these organisms. The reported No Observable Effect Concentration (NOEC) of 100 ul/L indicates no adverse effect at the 100 ul/L concentration, as opposed to an LC_{50} value at that same concentration. Our results are also in agreement with the results from the ECOSAR computer modeling program in EPIWIN which predict LC50 values of >777 mg/L for both species. Despite the absence of measurement of the actual exposure levels in the MIPK studies, they followed methods that were scientifically acceptable and robust for the date at which they were conducted (1988) and are well documented. Both studies were deemed as "Reliable with restrictions".

2. *"Algae.* Water hardness is the only missing data element and needs to be submitted if available."

A specific water hardness value was not detailed in the study report. Test media consisted of distilled water that was enriched with various salts according to OECD guidelines. The lack of this information does not impact the reliability of this study that was deemed as "Reliable without restrictions".

Health Effects (acute toxicity, repeat dose toxicity, genetic toxicity, and reproductive/developmental toxicity).

1. "Adequate test data are available for all health endpoints for the purposes of the HPV Challenge Program. However, the submitter needs to supply a robust summary for the reproductive toxicity endpoint. HPV Challenge Program guidance states that when a study addresses multiple endpoints, robust summaries are needed for each endpoint."

A robust summary for reproductive toxicity has been inserted.

2. *"Repeated-Dose Toxicity.* Although it is stated as "a full assortment of tissues," the submitter needs to define the specific tissues that were examined histopathologically."

The specific tissues examined have been added to the robust summary.

3. *Genetic Toxicity (in vitro).* In both summaries, the submitter needs to list concentrations that were tested. The submitter also needs to provide the number of replicate plates per concentration for the reverse mutation in bacteria study and the number of metaphases per concentration that were examined for the chromosomal aberration assay.

Since no evidence of genotoxicity was observed and both studies followed OECD guidelines only the maximum concentration tested was listed. Data have been reported in this manner without comment in other submissions. Information detailing the number of replicates per dose and cells counted has been added to the robust summaries.

Enclosed with this letter is a computer diskette containing the test plan and modified robust summaries in Adobe Acrobat (.pdf) format. The HPV registration number for Eastman Chemical Company is

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Technical Associate

Enclosure